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— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

(88) Date of publication of the international search report:
28 February 2008

(54) Title: PROTEIN KINASE MODULATION BY HOPS AND ACACIA PRODUCTS

(57) Abstract: Botanical compounds to modulate kinase activity are disclosed. The compounds and methods disclosed also inhibit expression of COX-2, inhibit synthesis of prostaglandins selectively in target cells, and inhibit inflammatory response selectively. The compositions contain at least one fraction isolated or derived from hops or *Acacia*.

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 06/47198

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 38/43; A61K 36/00 (2007.10)
USPC - 424/94.1; 424/725; 424/778
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC(8) - A61K 38/43 (2007.10)
USPC - 424/94.1, 424/725. 424/778

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
IPC(8) - A61K 38/43; A61K 36/00 (2007.10)
USPC - 424/94.1, 725, 778, 779, 775

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PubWest, DialogPRO, Google Patent, Google Scholar, PubMed/Medline, WIPO
Search Terms Used: , kinase, kinase activity, hops, Acacia, cox$, modulate, and combinations thereof.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X Y	US 2003/0180402 A1 (Jia et al.) 25 September 2003 (25.09.2003). Entirety. Esp., abstract, para [0014], [0023], [0032], [0062], [0072], [0078].	1-2, 10-13, 17-18, 26-29 3-9, 14-16, 19-25,30-34
Y	US 2005/0129791 A1 (Babish et al.) 16 June 2005 (16.06.2005). Esp., abstract, para [0019], [0060], [0119], [0120].	8,15,24,31,33-34
Y	US 2004/0115290 A1 (Tripp et al.) 17 June 2004 (17.06.2004). Esp., abstract, para [0061], [0062], [0063], [0066].	4-7, 20-23
Y	US 2005/0192356 A1 (Babish et al.) 1 September 2005 (01.09.2005). Esp., abstract, para [0016], [0017], [0080].	16,32
Y	US 2005/0042317 A1 (Babish et al.) 24 February 2005 (24.02.2005). Esp., abstract, para [0040].	14,30
Y	Ward et al., "Therapeutic Potential of Phosphoinositide 3-Kinase Inhibitors", Chemistry & Biology (March 2003) vol. 10, pages 207-213. Esp. page 209, para 3; page 210, para 1.	3,19
Y	Stevens et al., "Xanthohumol and Related Prenylflavonoids from Hops and Beer: to your good health", Phytochemistry (May 2004) vol. 65, page 1317 (Abstract only).	9,25

☐ Further documents are listed in the continuation of Box C. ☐

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
26 November 2007 (26.1.2007)	20 DEC 2007

Name and mailing address of the ISA/US	Authorized officer:
Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (April 2007)

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To: Toby H. Kusmer
McDermott Will & Emery LLP
28 State Street
Boston, MA 02109

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)*	20 DEC 2007
Applicant's or agent's file reference 068911-0173	FOR FURTHER ACTION See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US 06/47196	11 December 2006 (11.12.2006)	09 December 2005 (09.12.2005)

International Patent Classification (IPC) or both national classification and IPC
IPC(8) - A61K 38/43, 36/00 (2007.10)
USPC - 424/94.1; 424/725; 424/778

Applicant Metaproteomics, LLC

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA/US	Date of completion of this opinion	Authorized officer:
Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	26 November 2007(26.11.2007)	Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 06/47196

Box No. I Basis of this opinion

1. With regard to the language, this opinion has been established on the basis of:

   ☒ the international application in the language in which it was filed.

   ☐ a translation of the international application into _____ which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

2. ☐ This opinion has been established taking into account the rectification of an obvious mistake authorized by or notified to this Authority under Rule 91 (Rule 43*bis*.1(a))

3. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, this opinion has been established on the basis of:

   a. type of material

      ☐ a sequence listing

      ☐ table(s) related to the sequence listing

   b. format of material

      ☐ on paper

      ☐ in electronic form

   c. time of filing/furnishing

      ☐ contained in the international application as filed

      ☐ filed together with the international application in electronic form

      ☐ furnished subsequently to this Authority for the purposes of search

4. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

5. Additional comments:

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 06/47196

Box No. V **Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Claims	3-9, 14-16, 19-25, 30-34	YES
	Claims	1-2, 10-13, 17-18, and 26-29	NO
Inventive step (IS)	Claims	none	YES
	Claims	1-34	NO
Industrial applicability (IA)	Claims	1-34	YES
	Claims	none	NO

2. Citations and explanations:

Claims 1-2, 10-13, 17-18, and 26-29 lack novelty under PCT Article 33(2) as being anticipated by US 2003/0180402 A1 to JIA et al. (hereinafter 'JIA').

Regarding claims 1 and 17, JIA describes a method (para [0023]) and a composition (para [0033], [0035], [0056]), respectively, for modulating the activity of a plurality of disease associated protein kinases (abstract – COX-2 mediated diseases, para [0031]) in a subject in need thereof, wherein said protein kinase modulation is beneficial to the health of the subject (abstract; para [0031]); said method comprising administering (abstract) to the subject in need a therapeutically effective amount of a composition comprising a compound or extract derived from acacia (abstract, para [0023]).

Regarding claims 2 and 18, JIA teaches the method and composition of claims 1 and 17, respectively, for inflammatory disorders (para [0014]).

Regarding claims 10 and 26, JIA teaches the method and composition of claims 1 and 17, respectively, wherein the compound or extract is derived from Acacia nilotica (para [0014]).

Regarding claims 11 and 27, JIA teaches the method and composition of claims 1 and 17, respectively, wherein the Acacia nilotica compound is from Acacia nilotica extract (para [0014]).

Regarding claims 12 and 28, JIA teaches the method and composition of claims 1 and 17, respectively, wherein the Acacia catechu or Acacia nilotica extract is from acidified water(acidic), aqueous(polar) extractions (para [0062]), and organic extractions such as and ethyl acetate (para [0078]).

Regarding claims 13 and 29, JIA teaches the method and composition of claims 1 and 17, respectively, wherein pharmacologically acceptable excipients are employed that can be agents of color or absorption (para [0072]).

Claims 16 and 32 lack an inventive step under PCT Article 33(3) as being obvious over JIA, in view of US 2005/0192356 A1 to Babish et al. (hereinafter .BABISH'356.).

Regarding claims 16 and 32, refer to the teaching of JIA teaches as given above for claims 1 and 17, respectively. BABISH'356 further teaches a composition comprising extracts isolated from a natural plant (hops) wherein two different extracts (rho-isoalpha acid, RIAA; and isoalpha acid, IAA) are in a ratio of about 3:1 (para [0080]). These compounds exhibit anti-inflammatory action (abstract) influencing cycloxygenase enzymes and prostaglandin synthesis and inflammatory processes (para [0016], [0017]). Although BABISH.356 does not teach the use of acacia extracts, it was known that extracts of acacia also exhibit anti-inflammatory action, as taught by JIA (para [0014]). Based on the teachings of JIA, in view of BABISH'356, it would have been obvious to one of ordinary skill in the art through standard laboratory trial and experimentation to develop the method of claim 16 and composition of claim 32 comprising a 5:1 ratio of RIAA to Acacia nilotica heartwood powder extract. One would have been motivated to do so to develop a more effective method of treatment and would have had a reasonable level of anticipated success based on the teachings of JIA and BABISH'356.

Claims 8, 15, 24, 31, 33, and 34 lack an inventive step under PCT Article 33(3) as being obvious over JIA, in view of US 2005/0129791 A1 to Babish et al. (hereinafter 'BABISH'791').

Regarding claims 8 and 24, refer to the teachings of JIA as given above for claims 1 and 17, respectively. BABISH.791 further teaches the use of xanthohumol (para[0019]) in a formulation to provide anti-inflammatory effects (abstract).

Regarding claims 15 and 31, refer to the teachings of JIA as given above for claims 1 and 17, respectively. BABISH.791 further teaches the use of alpha and beta acids (para [0019]), as given above in claims 1 and 17, having anti-inflammatory effects (abstract) in the treatment of disorders such as diabetes (para [0060]). Based on the teachings of JIA, in view of the teachings of BABISH'791, it would have been obvious to one of ordinary skill in the art to develop a method and composition comprising an anti-diabetic drug. One would have been motivated to do so to develop a more effective synergistic composition for treatment and would have had a reasonable level of success based on the teachings of JIA and BABISH'791.

----------see continuatiuon sheet----------